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(54) New quinazolines as inhibitors of HIV reverse transcriptase.

(57) Compounds having a quinazolin-2-one nucleus with a substituted alkynyl or substituted alkenyl at the 4-position are described. These compounds are useful in the inhibition of HIV reverse transcriptase (including its resistant varieties), the prevention or treatment of infection by HIV and the treatment of AIDS, either as compounds, pharmaceutically acceptable salts, pharmaceutical composition ingredients, whether or not in combination with other antivirals, immunomodulators, antibiotics or vaccines. Methods of treating AIDS and methods of preventing or treating infection by HIV are also described.

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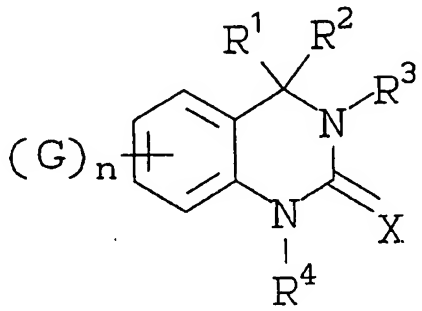
While the foregoing specification teaches the principles of the present invention, with examples provided for the purpose of illustration, it will be understood that the practice of the invention encompasses all of the usual variations, adaptations, or modifications, as come within the scope of the following claims and its equivalents.

Claims

1. A compound of the formula :



I

wherein:

X is O,

G, when present, is halo; nitro; or cyano;

n is 0-4;

R^1 is C_{3-5}cycloalkyl; C_{2-5} alkynyl, C_{2-4}alkenyl, or cyano;

R^2 is C_{2-5}alkynyl substituted with one or more of A, or C_{2-5} alkenyl substituted with one or more of A, wherein A is

i) halo,
ii) hydroxy,
iii) amino,
iv) cyano,
v) nitro,
vi) azido,
vii) C_{3-8} cycloalkyl,
viii) C_{1-4} alkoxy, unsubstituted or substituted with one or more of halo,
ix) di-(C_{1-4}alkyl) amino,
x) C_{1-4} alkylamino,
xi) aryl, unsubstituted or substituted with one or more of D, wherein D is amino, nitro, cyano, or C_{1-3} alkoxy,
xii) aryloxy, unsubstituted or substituted with one or more of D;
xiii) heterocycle, unsubstituted or substituted with one or more of D;
xiv) heterocycle-oxy;
xv) C_{2-5} alkenyl;
xvi) COOR, wherein R is H, C_{1-4}alkyl or aryl;
xvii) $CONR_2$; or
xviii) COR;

R_3 is

i) H;
ii) cyano;
iii) amino;
iv) hydroxyl;
v) C_{1-4} alkyl, unsubstituted or substituted with one or more of E, wherein E is halo, hydroxyl, amino, nitro, cyano, C_{1-4}-alkoxy, or C_{3-5} cycloalkyl;
vi) C_{2-4} alkenyl, unsubstituted or substituted with E; or

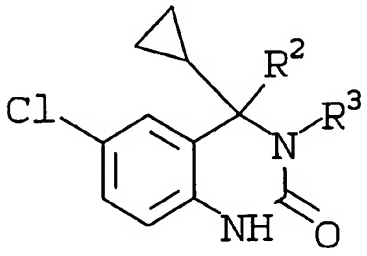
vii) C_{2-4} alkynyl, unsubstituted or substituted with E;

R_4 is

i) H;
ii) C_{1-4} alkyl;
iii) C_{1-5} alkylcarbonyl;
iv) benzoyl, unsubstituted or substituted with one or more of A; or
v) heterocyclecarbonyl;

with the proviso that any terminal alkynyl carbon is not substituted with any substituent selected from the group consisting of halo, hydroxy, amino, cyano, nitro, azido, C_{1-4}alkoxy unsubstituted or substituted with one or more of halo, di-(C_{1-4}alkyl)amino, C_{1-4}alkylamino, aryloxy unsubstituted or substituted with one or more of D, or heterocycle oxy;
or pharmaceutically acceptable salt thereof.

2. A compound according to Claim **1**, of the formula



II

wherein:

R^2 is C_{2-5} alkynyl substituted with halo, hydroxy, amino, cyano, nitro, azido, C_{3-8} cycloalkyl, C_{1-4} alkoxy, di-(C_{1-4} alkyl)amino, C_{1-4} alkylamino, phenyl, 2-nitrophenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, or C_{2-3} alkenyl;

R^3 is H or C_{1-3} alkyl;

or pharmaceutically acceptable salt thereof.

3. A compound which is
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-methoxy-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-(3-methoxy-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-(4-morpholinyl)-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-4-(4-fluoro-1-butynyl)-3,4-dihydro-3-methylquinazolin-2(1H)-one,
6-chloro-4-(4-chloro-1-butynyl)-4-cyclopropyl-3,4-dihydro-3-methylquinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-4-(4-fluoro-1-butynyl)-3,4-dihydroquinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-4-(3-fluoro-1-propynyl)-3,4-dihydro-3-methylquinazolin-2(1H)-one,
4-(3-azido-1-propynyl)-6-chloro-4-cyclopropyl-3,4-dihydro-3-methylquinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-(3-(1-imidazolyl)-1-propynyl)-3-methylquinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-)2,2,-2,-trifluoroethoxy)-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-(4-pyridyloxy)-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-(4-(N-oxopyridyl)oxy)-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((3-pyridyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((4-pyridyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((2-pyrazinyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((5-pyrimidinyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-((2-pyridyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((2-pyrimidinyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-(N,N-dimethylamino)-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-(phenylethynyl)quinazolin-2(1H)-one,
4-(3-buten-1-ynyl)-6-chloro-4-cyclopropyl-3,4-dihydro-3-methylquinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-(3-hydroxy-1-propynyl)-3-methylquinazolin-2(1H)-one,

6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-(3-(2-pyridyloxy)-1-propynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((2-nitrophenyl)ethynyl)quinazolin-2(1H)-one, or
6-chloro-4(S)-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2(1H)-one,
or pharmaceutically acceptable salt thereof.

4. A compound of Claim 3, which is
6-chloro-4-cyclopropyl-4-(4-fluoro-1-butynyl)-3,4-dihydro-3-methylquinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-3-methyl-4-((2-pyridyl)ethynyl)quinazolin-2(1H)-one,
6-chloro-4-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2(1H)-one;
6-chloro-4-cyclopropyl-3,4-dihydro-4-(phenylethynyl)quinazoin-2(1H)-one, or
6-chloro-4(S)-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2(1H)-one.
or pharmaceutically acceptable salt thereof.

5. The synergistic combination of 6-chloro-4(S)-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2-(1H)-one, and ddI.

6. The synergistic combination of 6-chloro-4(S)-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2-(1H)-one, and AZT.

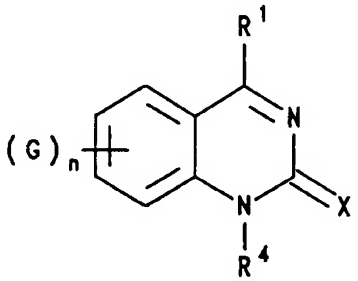
7. The synergistic combination of 6-chloro-4(S)-cyclopropyl-3,4-dihydro-4-((2-pyridyl)ethynyl)quinazolin-2-(1H)-one, and N-(2(R)-hydroxy-1(S)-indanyl)-2(R)-phenylmethyl-4-(S)-hydroxy-5-(1-(4-(3-pyridylmethyl)-2(S)-N'-(t-butylcarboxamido)-piperazinyl))-pentanemamide.

8. The use of a compound as claimed in any of Claims 1-4 for the manufacture of a medicament for inhibiting HIV reverse transcriptase.

9. The use of a compound as claimed in any of Claims 1-4 for the manufacture of a medicament for preventing infection of HIV, or of treating infection by HIV or of treating AIDS or ARC.

10. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound as in any of Claims 1-4, or an effective amount of a synergistic combination as in any of claims 5-7.

11. A process for the preparation of a compound as claimed in Claim 1, which process comprises reaction of an intermediate of formula (III)



(III)

wherein R^1, R^4, G, n and X are as defined for formula (I), or a protected derivative thereof, with a reagent suitable to introduce the group R^2 or a group convertible thereto, followed, if necessary, by deprotection; and optionally converting the compound of formula (I) so prepared to another compound of formula (I).